the respective values of 0.39 versus 0.51 mg/dL, although statistically different, are not clinically different.

It should be clearly noted that our study was not performed to demonstrate the efficacy of aprotinin in pediatric patients. There have been numerous previous studies to indicate that aprotinin is indeed efficacious in pediatric patients undergoing CPB. A recent meta-analysis by Arnold and colleagues[20] reported that aprotinin reduced the proportion of children who received red blood cell or whole blood transfusions during cardiac surgery by 33%. Our own study published in 2003 demonstrated that with the use of aprotinin, children were exposed to 3 instead of 5 red blood cell units. Operative closure time was less (ie, 93 vs 127 minutes, a savings of 34 minutes). The Ann Arbor group in 1996 reported in a prospective, randomized, placebo-controlled, double-blind trial that aprotinin resulted in fewer exposures to bank-blood components and was also associated with a savings in the patient charges for blood components, operating room time, and duration of hospitalization.[8] The group from Eggleston Children's Hospital in 1998 reported similar findings.[9]

A recent study at the University of California, San Francisco, evaluated the use or nonuse of aprotinin in patients undergoing the Norwood, Glenn, and Fontan procedures. The authors concluded the following: "The key point of these data is that we did not see evidence of clinical concern in this population of children with . . . aprotinin. If anything our data support the safety of these drugs for use in children undergoing the repair of congenital cardiac defects."[21] The Milwaukee group, in particular, has demonstrated the utility and safety of aprotinin use and reuse in pediatric patients undergoing cardiothoracic procedures.[22,23] They concluded that the risk of hypersensitivity reactions to aprotinin is low (approximately 1%), even with multiple exposures to the medication. Our analysis of the risk of re-exposure confirms the Milwaukee analysis; we had no adverse responses in 94 patients re-exposed within 1 year.

In our study of 2090 pediatric patients undergoing CPB, there was no association between the use of high-dose aprotinin and operative or late mortality, biochemical acute kidney failure, need for temporary dialysis, or neurologic complications. Given the previous studies demonstrating its efficacy, we continue to use aprotinin in all pediatric patients undergoing CPB.

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## Discussion

**Dr James S. Tweddell** (*Milwaukee, Wis*). That was an excellent presentation, Carl, as usual. This is a timely contribution from the group at Children's Memorial Hospital. The authors looked at their entire experience with aprotinin, a period of 6 years, and compared this with the previous 6-year period. Just over 2000 patients are

included, pretty much evenly divided between the use and nonuse of aprotinin, making this the largest single-center report concerning aprotinin use in pediatrics by far.

Despite an increase in case complexity in the most recent aprotinin cohort, there is no difference in mortality or renal impairment, suggesting that aprotinin use is safe in this age group. Incidentally, our aprotinin use policy is identical to yours.

The limitations of this study have been acknowledged by the authors and most importantly include the comparison of noncontemporary patient groups. I would contend that this is a form of selection bias.

This study begins in 1994, and just for some perspective, in 1994, the sitcom "Friends" premiered on NBC, Netscape 1.0 was released, and George Bush was unequivocally elected governor of Texas. Times have changed.

Since 1994, we have seen some important changes in various aspects of preoperative, intraoperative, and postoperative management of patients with congential heart disease, including some pioneered from your institution.

Taking the devil's advocate position, one could argue that your most recent results, which are excellent, would have been even better if you had not used aprotinin. Therefore my comments and questions are really directed at potential ways around this time–bias issue.

The most recent studies from the Ischemia Research and Education Foundation purported to show that aprotinin use was associated with a significantly increased risk of complications in adults—myocardial infarction, stroke and renal failure—in patients not having complex operations. Could you or did you analyze the effect of aprotinin risk within risk stratification categories? You could divide your patient population above and below the 50th percentile Aristotle score, for example, and this would be a way to match aprotinin use and risk stratification. Perhaps the risk/benefit ratio of aprotinin is favorable for high-risk patients but not so for low-risk patients. You had these data, and I think this would make an additional excellent analysis, and I would like to hear your comments on that.

**Dr Backer.** We did try to look at risk stratification based on Aristotle scores. We were particularly interested in the group of patients who required postoperative temporary dialysis because those were the patients who clearly had substantial kidney failure. The mean Aristotle score in the no-aprotinin group that required dialysis was 7.67. All of these patients had difficult operations, such as tricuspid valve replacement after heart transplantation and disrupted aortic annulus with emergency operation.

The mean Aristotle score in the aprotinin group that required dialysis was 10.08, a high score that was almost statistically higher than that of the other group. If you look at this patient population, again, all these patients were at very high risk. There was a Fontan conversion with an Aristotle score of 12, there were 2 patients in heart transplantation status after Fontan conversion, there was a transplantation after a ventricular assist device, and there was a patient with a switch with an intramural coronary artery who was on extracorporeal membrane oxygenation. We did not have any patient who had, for example, a straightforward ventricular septal defect closure and then had kidney failure.

The other part of the data to look at is the multivariate analysis of biochemical acute kidney failure. The mean Aristotle score in the group without acute kidney failure was 7.5, and in those with acute kidney failure, it was 8.5. The Aristotle score only trended to significance, with a $P$ value of .063. In the patients who required postoperative temporary dialysis, where the Aristotle score was statistically significant ($P < .001$), it was 7.5 in the patients who did not require dialysis and 9.3 in the patients who did require postoperative dialysis.

However, your point is well taken, and we could incorporate risk stratification as a specific subanalysis of the data.

**Dr Tweddell.** Those are certainly compelling data, but I would suggest that it might be worthwhile performing the analysis.

Concerning the incidence of renal insufficiency, as determined based on chemical data, interestingly, the preoperative creatinine level was less in patients who sustained postoperative biochemical renal dysfunction, at least the way you defined it. This really causes me to question the validity of this definition. I know you used the somewhat arbitrary definition that was developed by the Society of Thoracic Surgeons in the multidisciplinary working group, and the purpose of that is really to allow some multi—institutional comparisons. Because this is a single-institution study and because I am certain Children's Memorial has age—specific creatinine ranges of normalcy, you could actually analyze that separately. I think that would be important because that is obviously an important conclusion of your article.

**Dr Backer.** That is a good point. We discussed with our pediatric nephrologists what definition we should use for acute kidney failure. One of the problems with taking the absolute value is that if a sick patient's preoperative creatinine level is increased, for instance to 1.5 times normal value, then a postoperative level of 1.5 times normal value is not a change. The Society of Thoracic Surgeons–European Association for Cardiothoracic Surgery definition of acute kidney failure is a doubling of the creatinine level compared with the preoperative value or a level that is 1.5 times normal value, but the doubling seemed to take precedence for this reason. Our pediatric nephrologists believed that using doubling of the preoperative creatinine level as our definition would "widen the net," so that we would not miss patients with borderline postoperative kidney failure.

You noted, as we did in the article, that in the multivariate analysis there was the counterintuitive finding that the preoperative creatinine level was 0.51 mg/dL in the patients who did not have acute kidney failure, and it was 0.39 mg/dL in the patients who did have acute kidney failure. The question here is whether a creatinine level of 0.5 versus 0.4 mg/dL is actually clinically relevant.

In contrast, for those patients who required postoperative temporary dialysis, the association of preoperative creatinine level was significant, with a $P$ value of .03. The patients who did not require temporary dialysis had a mean preoperative creatinine level of 0.5 mg/dL. If they did require temporary dialysis, the mean preoperative value was 0.9 mg/dL. Therefore in the subgroup with kidney failure requiring postoperative dialysis, they did have a higher preoperative creatinine level, almost twice as high as before the operation.

**Dr Tweddell.** I guess I was suggesting that you use the most inclusive definition because that is important to rule it out. Also, I think that is more important than the application of dialysis because that is really measuring a clinical response and not necessarily biochemical evidence of renal failure.

I have just a couple of other questions. Aprotinin is a strong inhibitor of bradykinin generation. Bradykinin is implicated in perioperative neurologic injury. Did you look at neurologic complications, seizures, and new deficits?

**Dr Backer.** We do have neurologic data in our database, although we did not specifically look at it. We could go back and analyze that relatively easily. However, we do not currently have late follow-up on neurologic outcomes.

**Dr Tweddell.** Have you had incidents of anaphylaxis, and how do you re-expose? Do you re-expose patients within a year?

**Dr Backer.** We relied on your article in *Circulation* that suggested that it was safe to redose aprotinin. The main group undergoing re-exposure within a year consisted of those who had the Norwood procedure with aprotinin and then within 4 to 6 months had the bidirectional Glenn procedure. Initially, our anesthesiologists were hesitant to use aprotinin during the Glenn procedure. Your article came out with the less than 1% anaphylaxis, and therefore currently, we administer aprotinin at the Norwood and Glenn procedures, irrespective of whether they have their Glenn procedure at 3.5, 4, or 6 months, and again at the Fontan procedure.

Our primary safety protocol is that every patient gets a test dose of aprotinin, and we wait to do that until the arterial line and the central line are in. We have had one patient who had significant hypotension related to the aprotinin—just one patient out of this entire group.

**Dr Tweddell.** Obviously there are no indications for aprotinin use in pediatrics, but there is now a black box warning about re-exposure within a year.

**Dr Backer.** Yes.

**Dr Tweddell.** It is one thing to use it when there is not an indication, and it is another thing to use it against a black box warning. I wonder if you have changed your policy at all? I think we are struggling with that as well.

**Dr Backer.** We have not changed our policy. The Friday before I came here, I did a reoperation to do a shunt revision on a patient after the Norwood procedure. We had used aprotinin 10 days earlier, and I used aprotinin again, and nothing happened. Granted, it is only 1 patient.

**Dr Tweddell.** My last and final question is whether you think we need a postmarket randomized controlled trial in pediatrics to approve efficacy and safety?

**Dr Backer.** Well, I think in an ideal world that would be a good thing. I think if there are enough questions about this and if centers are unable to use aprotinin because of the negative press and because of parental concerns, a randomized prospective study might be the only way we are going to prove its safety. There have been several studies that have showed efficacy, and we could look at efficacy and safety in the prospective trial. Specifically, we could look at kidney function and even do some more in-depth analysis, such as postoperative GFR and postoperative urine collections for creatinine clearance.

**Dr Tweddell.** Thank you. Excellent article.

**Dr Kenneth G. Warner** (*Boston, Mass*). Did you see any increased incidence of thrombotic complications in the aprotinin group, such as strokes, premature closure of fenestrations, and deep vein thrombosis?

**Dr Backer.** No. I mean, we have almost no thrombosis in our patients and that was not—we did not see that.